We Claim:

1. A method for sequence analysis of one or more target nucleic acids for which a reference nucleic acid sequence is known, the method comprising the steps of:

(a) deriving from one or more biological samples the one or more target nucleic acids;

(b) subjecting the one or more target nucleic acid to complementary cleavage reactions with one or more cleavage reagents thereby generating cleavage products;

(c) performing mass spectroscopical analysis on the cleavage products generated in step (b) to obtain one or more mass spectra; and

(d) comparing the one or more mass spectra of the cleavage products of the one or more target nucleic acids obtained in step c) with a known or predicted mass spectra for the reference nucleic acid sequence, and deducing therefrom, by systematic computational analysis, all or part of the nucleotide sequence of the one or more target nucleic acids, and comparing the deduced nucleic acid sequence with the reference nucleic acid to determine whether the one or more target nucleic acids have the same sequence or a different sequence from the reference nucleic acid.

2. The method of claim 1 wherein the nucleic acid sequence difference that is determined in step d) is a deletion, substitution, insertion or combinations thereof.

3. The method of claim 1 wherein the biological sample is derived from organism selected from the group consisting of eukaryotes, prokaryotes, and viruses.

4. The method of claim 1 wherein the target nucleic acid is selected

from the group consisting of single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, and DNA/RNA mosaic nucleic acid.

5. The method of claim 4 wherein the one or more target nucleic acids is derived by one or more consecutive amplification procedures selected from the group consisting of *in vivo* cloning, polymerase chain reaction (PCR), reverse transcription followed by the polymerase chain reaction (RT-PCR), strand displacement amplification (SDA), and transcription based processes.

6. The method of claim 5 wherein the one or more amplified target nucleic acids are RNA transcripts generated from a single stranded or a double stranded target nucleic acid by a process comprising the steps of:

(a) linking operatively an expression control sequences to the one or more target nucleic acids; and

(b) transcribing one or both strands of the one or more target nucleic acid of step a) using one or more RNA polymerases that recognize the transcription control sequence on the one or more target nucleic acids.

7. The method of claim 6 wherein the transcription control sequence is selected from the group consisting of an eukaryotic transcription control sequence, a prokaryotic transcription control sequence, and a viral transcription control sequence.

8. The method of claim 7 wherein the prokaryotic transcription control sequence is selected from the group consisting of T3, T7, and SP6 promoters.

9. The method of claim 8 wherein the RNA polymerases which utilize the T3, T7, or SP6 promoters are either wild type or mutant RNA polymerases,

the mutant polymerases being capable of incorporating into the RNA transcript non-canonical substrates with a 2′-substituent other than a hydroxyl group.

10. The method of claims 4, 5, 6, 7, 8 or 9 wherein the target nucleic acid is derived using one or more modified nucleoside triphosphates selected from the group consisting of mass modified deoxynucleoside triphosphates, mass modified dideoxynucleoside triphosphates, and mass modified ribonucleoside triphosphates.

11. The method of claim 10 wherein the modified nucleoside triphosphates are modified on the base, sugar, and/or the phosphate moiety, and are introduced through an enzymatic step, chemically, or a combination of both.

12. The method of claim 10 wherein the modification consists of 2′-substituents other than a hydroxyl group on the nucleotide triphosphates.

13. The method of claim 10 wherein the modification consists of phosphorothioate internucleoside linkages or phosphorothioate internucleoside linkages further reacted with an alkylating reagent.

14. The method of claim 10 wherein the modification consists of a methyl group on C5 of the uridine-5′-monophosphate subunits.

15. The method of claim 10 wherein the modifications alter the specificity of cleavage by the one or more cleavage reagents and/or the mass and/or the length of the cleavage products.

16. The method of claims 11, 12, 13 or 14 wherein the modifications alter the specificity of cleavage by the one or more cleavage reagents and/or the mass and/or the length of the cleavage products.

17. The method of claim 1 wherein the complementary cleavage reactions are selected from the group consisting of enzymatic cleavage, chemical cleavage, and physical cleavage.

18. The method of claim 17 wherein the complementary cleavage reactions are characterized by a relaxed mono-nucleotide, mono-nucleotide, relaxed di-nucleotide, or di-nucleotide specificity.

19. The method of claim 17 or claim 18 wherein the chemical cleavage reaction consists of an alkali treatment, and the one or more target nucleic acids are RNA transcripts that have incorporated non-canonical substrates with a 2′-substituent other than a hydroxyl group.

20. The method of claim 17 or claim 18 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more enzymes selected from the group consisting of endonucleases and exonucleases.

21. The method of claim 20 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more endonucleases, selected from the group consisting of restriction enzymes, RNA endonucleases, DNA endonucleases and non-specific phosphodiesterases.

22. The method of claim 21 wherein the one or more endonucleases are one or more selective or non-selective RNA endonucleases and the one or more target nucleic acids are transcripts.

23. The method of claim 22 wherein the one or more selective or non-selective RNA endonuclease is selected from the group consisting of the G-specific T_1

ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin.

24. The method of claim 15 wherein the one or more target nucleic acids are phosphorothioate-modified single-stranded DNA or RNA and the endonuclease is nuclease P1.

25. The method of claim 1 wherein the mass spectroscopical analysis of the nucleic acid fragments is performed using a mass spectroscopic method selected from the group consisting of Matrix-Assisted Laser Desorption/Ionization-Time-of-flight (MALDI-TOF), Electrospray-Ionization (ESI), and Fourier Transform-Ion Cyclotron Resonance (FT-ICR).

26. A method for scoring known nucleotide sequence variations of one or more target nucleic acids for which a known reference nucleic acid sequence is available, the method comprising the steps of:

(a) deriving from one or more biological samples the one or more target nucleic acids;

(b) subjecting the one or more target nucleic acids to complementary cleavage reactions with one or more cleavage reagents thereby generating cleavage products;

(c) performing mass spectroscopical analysis on the cleavage products obtained in step (b) to obtain two or more mass spectra; and

(d) comparing the one or more mass spectra of the cleavage products of the one or more target nucleic acids obtained in step c) with the known or predicted mass spectra for the reference nucleic acid sequence, and scoring therefrom, by systematic computational analysis the presence or absence of the known nucleotide sequence variations of the one or more target nucleic acids.

27. The method of claim 26 wherein the nucleic acid sequence variation of the target nucleic acid scored in step d) is a deletion, a substitution, insertion or combinations thereof.

28. The method of claim 26 wherein the one or more target nucleic acids are derived from biological samples selected from the group consisting of an eukaryote, a prokaryote, and a virus.

29. The method of claim 26 or claim 27 wherein the one or more target nucleic acids are selected from the group consisting of a single stranded DNA, a double stranded DNA, a single stranded RNA, a double stranded RNA, and a DNA/RNA hybrid.

30. The method of claim 29 wherein the one or more target nucleic acids are derived by one or more consecutive amplification procedures selected from the group consisting of *in vivo* cloning, the polymerase chain reaction (PCR), reverse transcription followed by the polymerase chain reaction (RT-PCR), strand displacement amplification (SDA), and transcription based processes.

31. The method of claim 29 wherein the one or more amplified target nucleic acids are RNA transcripts generated by a process comprising the steps of:

(a) linking operatively a transcription control sequences to the one or more target nucleic acids; and

(b) transcribing one or both strands of the one or more target nucleic acids using one or more RNA polymerases that recognize the transcription control sequence on the one or more target nucleic acids.

32. The method of claim 31 wherein the transcription control sequence

is selected from the group consisting of an eukaryotic transcription control sequence, a prokaryotic transcription control sequence, and a viral transcription control sequence.

33. The method of claim 32 wherein the prokaryotic transcription control sequence is selected from the group consisting of T3, T7, or SP6 promoters.

34. The method of claim 33 wherein the RNA polymerases which utilize the T3, T7 or SP6 promoters are either wild type or in a mutant form capable of incorporating non-canonical substrates with a 2′-substituent other than a hydroxyl group.

35. The method of claim 30, 31 or 32 wherein the one or more target nucleic acids are derived using a modified nucleoside triphosphates selected from the group consisting of mass modified deoxynucleoside triphosphates, mass modified dideoxynucleoside triphosphates, and mass modified ribonucleoside riphosphates.

36. The method of claim 35 wherein the modified nucleoside triphosphates are modified on the base, sugar, and/or the phosphate moiety, and are introduced through an enzymatic step, chemically, or a combination of both.

37. The method of claim 35 wherein the modification consists of 2′-substituents other than a hydroxyl group on the nucleoside triphosphates.

38. The method of claim 35 wherein the modification consists of phosphorothioate internucleoside linkages or phosphorothioate internucleoside linkages further reacted with an alkylating reagent.

39. The method of claim 35 wherein the modification consists of a methyl group on C5 of the uridine-5′-monophosphate subunits.

40. The method of claim 35 wherein the modifications alter the specificity of cleavage by the one or more cleavage reagents and/or the mass and/or the length of the cleavage products.

41. The method of claim 36, 37, 38, 39 or 40 wherein the modifications alter the specificity of cleavage by the one or more cleavage reagents and/or the mass and/or the length of the cleavage products.

42. The method of claim 26 wherein the complementary cleavage reactions are from the group consisting of enzymatic cleavage, chemical cleavage, and physical cleavage.

43. The method of claim 42 wherein the complementary cleavage reactions are characterized by a relaxed mono-nucleotide, mono-nucleotide, relaxed di-nucleotide, or di-nucleotide specificity.

44. The method of claim 42 or claim 43 wherein the chemical cleavage consists of an alkali treatment, and the one or more target nucleic acids are RNA transcripts that incorporate non-canonical substrates with a 2′-substituent other than a hydroxyl group.

45. The method of claim 42 or claim 43 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more enzymes selected from the group consisting of endonucleases and exonucleases.

46. The method of claim 45 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more endonucleases, selected from the group consisting of restriction enzymes, RNA endonucleases, DNA

endonucleases, and non-specific phosphodiesterases.

47. The method of claim 46 wherein the one or more endonucleases are the one or more selective or non-selective RNA endonucleases and one or more target nucleic acids are transcripts.

48. The method of claim 46 or claim 47 wherein the one or more RNA endonucleases are selected from the group consisting of the G-specific T_1 ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin.

49. The method of claim or claim wherein the one or more target nucleic acids are phosphorothioate- modified single-stranded DNA or RNA and the endonuclease is nuclease P1.

50. The method of claim 26 wherein the mass spectroscopical analysis of the nucleic acid fragments is performed using a mass spectroscopic method selected from the group consisting of Matrix-Assisted Laser Desorption/Ionization-Time-of-flight (MALDI-TOF), Electrospray-Ionization (ESI), and Fourier Transform-Ion Cyclotron Resonance (FT-ICR).

51. A method for determining the sequence of one or more target nucleic acids, the method comprising the steps of:

(a) deriving from a biological sample material the one or more target nucleic acids;

(b) subjecting the one or more target nucleic acids to complementary cleavage reactions with one or more cleavage reagents thereby generating cleavage products;

(c) performing mass spectroscopical analysis on the cleavage products obtained in step (b) to obtain a mass spectra of the nucleic acid fragments; and

(d) deducing therefrom the nucleotide sequence of the one or more target nucleic acids by systematic computational analysis on the mass spectra of the cleavage products obtained in step (c).

52. A method for genome wide genotyping of one or more known or unknown target nucleic acids, the method comprising the steps of:

(a) deriving from one or more biological samples the one or more target nucleic acids;

(b) subjecting the one or more target nucleic acids to one or more specific cleavage reactions with one or more cleavage reagents thereby generating cleavage products;

(c) performing mass spectroscopical analysis on the cleavage products obtained in step (b) to obtain one or more mass spectra; and

(d) comparing the mass spectra of the cleavage products obtained in step c) with reference mass spectra, and diagnosing therefrom genetically relevant nucleic acid sequence variations of the one or more known or unknown target nucleic acids.

53. A method for identifying one or more target nucleic acids in one or more biological samples, the method comprising the steps of:

(a) deriving from one or more biological samples the one or more target nucleic acids;

(b) subjecting the one or more target nucleic acids of step (a) to one or more specific cleavage reactions with one or more cleavage reagents thereby generating cleavage products;

(c) performing mass spectroscopical analysis on the cleavage

products obtained in step (d) to obtain one or more mass spectra; and

(d) comparing the one or more mass spectra obtained in step c) with each other or with a plurality of mass spectra of reference nucleic acids, and deducing therefrom the identity of the one or more target nucleic acids.

54. The method of claim 53 wherein the one or more target nucleic acids are cDNA.

55. The method of claim 54 wherein the method is used to determine the expression profile in a biological sample.

56. A kit for sequence analysis of one or more target nucleic acids using mass spectroscopy, the kit comprising:

(a) one or more sets of reference nucleic acids for which the nucleic acid sequence is known;

(b) one or more nucleotide triphosphates;

(c) one or more polymerases;

(d) one or more nucleic acid cleaving agents; and

(e) computer software for comparing the mass spectra of the one or more target nucleic acid with the mass spectra of the reference nucleic acid and deducing therefrom the nucleic acid sequence of the target nucleic acid.